REMARKS

Applicants file this Amendment in response to the Office Action mailed July 7, 2008. The Office Action set an initial due date for response of October 7, 2008, and thus no fee is believed due at this time.

In the Action, the Office considers and rejects claims, 1-2, 4-8, 10-14, 16, and 17. The present Amendment amends claim 7; cancels claims 1-2, 4-6, and 16; and adds new claims 20-25. Claims 7-8, 10-14, 17, and 20-25 are pending and under consideration. The amendment of the claims finds support in the specification as filed, e.g., at page 5, lines 3-7; page 7, lines 8-19; page 9, lines 2-14; paragraph bridging pages 8-9; page 11, line 13 through page 12, line 9; and Test Examples 1-11 on pages 13-16.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

The Office Action rejects claims 7-8, 10-14, and 16-17 under 35 U.S.C. § 112, first paragraph as allegedly filing to comply with the written description requirement. In particular, the Office Action states that the Examiner "could not find support within the specification for the new limitation found within claim 7 which states that the mixture is suspended in a **non-aqueous solution**" (emphasis in original).

In response, and without acquiescing to the propriety of any of the assertions made in the rejection of the claims under 35 U.S.C. § 112, first paragraph, Applicants respectfully submit that the amendment addresses the instant rejection and respectfully request withdrawal of the same.

Claim Rejections – 35 U.S.C. § 102(b)

The Office Action rejects claims 1-2, 4-8, 10-12, 14, and 16-17 under 35 U.S.C. § 102(b) as allegedly anticipated by Scott et al. (WO 01/28524; hereinafter SCOTT). In particular, the Office Action states that SCOTT teaches sustained release microspheres and the method to produce them, the microspheres comprising a macromolecule (including therapeutic proteins), a water soluble polymer, and preferably a complexing agent (including sulfated dextran, heparin and chondroitin). The Office Action further states that SCOTT teaches such sustained release microparticles further coated by compounds such as fatty acids and lipids.

In response, and without acquiescing to the propriety of any of the assertions made in the rejection of the claims under 35 U.S.C. § 102(b), Applicants respectfully submit that the amendment addresses the instant rejection and respectfully request withdrawal of the same. Applicants further submit that the claimed subject matter is not anticipated by SCOTT at least because SCOTT does not disclose "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide,

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof, and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." Neither does SCOTT disclose "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide, and further adding a protein stabilizer to the mixture;

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof; and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." In particular, Applicants submit that SCOTT does not teach formation of a complex of the protein and the sulfated polysaccharide at room temperature in a process consisting essentially of the method steps set forth above.

In contrast, SCOTT teaches a method for forming a microsphere comprising: (1) forming an aqueous mixture containing: (a) a carrier protein; (b) a water soluble polymer; (c) a first complexing agent that is a polyanionic polysaccharide; and (d) a second complexing agent that is a divalent metal cation selected from the group consisting of calcium and magnesium; (2) allowing the microspheres to form in the aqueous mixture; and (3) stabilizing the microspheres, preferably by contacting the microspheres with a cross-linking agent and/or exposing the microspheres to an energy source, preferably heat, under conditions sufficient to stabilize the microspheres (see, e.g., SCOTT at claim 19, pages 59-60). While SCOTT does disclose mixture

of proteins and dextran sulfate for transient periods of time at ambient temperature, e.g. at page 54 (Example 16), SCOTT further discloses addition of aqueous solution of polymer and incubation at, e.g., 37°C to 50°C, and then a stabilization step which can include heating to a temperature of, e.g., between 70°C to 100°C or the addition of a chemical stabilizer (SCOTT at paragraph bridging pages 33-34; and page 54, Example 16).

For at least the foregoing reasons, Applicants submit that the instant claims are not anticipated by SCOTT and respectfully request withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 102(e)

The Office Action also rejects claims 1-2, 4-8, 10-14, and 16-17 under 35 U.S.C. § 102(e) as allegedly anticipated by Straub et al. (U.S. Patent No. 6,932,983; hereinafter STRAUB). In particular, the Office Action states that STRAUB discloses porous drug matrices and methods of manufacturing the same, wherein the matrices are preferably in the form of microparticles. The Office Action further states that the matrices incorporate numerous drugs including therapeutically useful proteins (which can be encapsulated by a pegylated phospholipid), and which further comprises excipients including hydrophilic polymers such as dextran sulfate, sugars, and wetting agents which include stearic acid, wax, and sorbitan fatty acid esters such as TWEEN.

In response, and without acquiescing to the propriety of any of the assertions made in the rejection of the claims under 35 U.S.C. § 102(e), first paragraph, Applicants respectfully submit that the amendment addresses the instant rejection and respectfully request withdrawal of the same. Applicants further submit that the claimed subject matter is not anticipated by STRAUB

at least because STRAUB does not disclose "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide,

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof, and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." Neither does STRAUB disclose "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide, and further adding a protein stabilizer to the mixture;

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof; and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." In particular, Applicants submit that STRAUB does not

teach formation of a complex of the protein and the sulfated polysaccharide at room temperature in a process consisting essentially of the method steps set forth above.

In contrast, STRAUB teaches drug matrices made using a process that includes (i) dissolving a drug, preferably a drug having low aqueous solubility, in a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion, suspension, or second solution, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug (see STRAUB Abstract). Furthermore, STRAUB teaches such drug matrices for the purpose of enhancing the rate of dissolution, not for sustained release (see STRAUB, e.g., at col. 1, lines 14-17).

For at least the foregoing reasons, Applicants submit that the claims are not anticipated by STRAUB and respectfully request withdrawal of this rejection.

Claim Rejections - 35 U.S.C. § 103(a)

The Office Action also rejects claims 1-2, 4-8, 10-14, and 16-17 under 35 U.S.C. § 103(a) as allegedly unpatentable over SCOTT. In particular, the Office Action states that since SCOTT allegedly describes that spray drying is routinely used in the art to dry microparticles, it would have been obvious to the skilled artisan that spray drying could be used to dry the microparticles recited.

In response, Applicants submit that the claimed and disclosed invention is not unpatentable over SCOTT. For at least the reasons set forth above in response to the rejection of claims 1-2, 4-8, 10-12, 14 and 16-17 under 35 U.S.C. § 102(b), SCOTT fails to anticipate or to suggest the claimed and disclosed invention. Additionally, Applicants submit that the instant

invention has advantages over the disclosure of SCOTT. In the process of the present invention, proteins are combined with sulfated polysaccharides at room temperature to form a complex. Accordingly, the presently claimed invention prevents degradation or denaturation of the protein drug, and increases yield.

Moreover, there is nothing in SCOTT that would have led to the particular choice of spray drying as the Office asserts. The Office's assertion is simply without support.

In view of the foregoing remarks, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, and respectfully request withdrawal of the rejection under 35 U.S.C. 103(a).

The Office Action also rejects claims 1-2, 4-8, 10-14, and 16-17 under 35 U.S.C. § 103(a) as allegedly unpatentable over SCOTT in view of STRAUB. In particular, the Office Action states that SCOTT is silent with regard to forming the micropheres described therein in a non-aqueous solution. The Office relies upon STRAUB for this missing feature.

In response, and without acquiescing to the propriety of any of the assertions made in the rejection of the claims under 35 U.S.C. § 103(a), Applicants respectfully submit that the amendment addresses the instant rejection and respectfully request withdrawal of the same. Applicants further submit that the claimed subject matter is not unpatentable over SCOTT in view of STRAUB for at least the reasons set forth above. In particular, Applicants submit that neither SCOTT nor STRAUB, either alone or in combination, disclose or fairly suggest "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide,

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof, and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." Neither do SCOTT and/or STRAUB, either alone or in combination disclose or fairly suggest "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide, and further adding a protein stabilizer to the mixture;

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof; and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." Neither do SCOTT and/or STRAUB, either alone or in combination disclose or fairly suggest "[a] sustained release solid formulation characterized by consisting essentially of protein drug, sulfated polysaccharide, and hydrophobic material selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof,

wherein the mixture of protein and sulfated polysaccharide is encapsulated within a matrix of the hydrophobic material, and the sustained release solid formulation is prepared by the process of claim 7."

For at least the reasons set forth above, SCOTT and/or STRAUB fail to fairly suggest the claimed invention.

In view of the foregoing remarks, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, and respectfully request withdrawal of the rejection under 35 U.S.C. 103(a).

The Office Action also rejects claims 1-2, 5-8, 11-14, and 16-17 under 35 U.S.C. § 103(a) as allegedly unpatentable over Edwards et al. (U.S. Patent No. 5,985,309; hereinafter EDWARDS). In particular, the Office Action states that EDWARDS discloses micronized particles for inhalation, wherein the particles incorporate a surfactant and/or hydrophobic complex of a positively or negatively charged therapeutic agent (including proteins) in combination with a charged molecule of opposite charge, and a complex-forming material (including dextran sulfate). The Office Action further states that EDWARDS discloses that the particle material can be manufactured from fatty acids, the surfactants included phospholipids and fatty acids, and other excipients such as sugars could also be included in the composition.

In response, and without acquiescing to the propriety of any of the assertions made in the rejection of the claims under 35 U.S.C. § 103(a), Applicants respectfully submit that the amendment addresses the instant rejection and respectfully request withdrawal of the same. Applicants further submit that the claimed subject matter is not unpatentable over EDWARDS.

In particular, Applicants submit that EDWARDS does not disclose "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide,

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof, and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." Neither does EDWARDS disclose or fairly suggest "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide, and further adding a protein stabilizer to the mixture;

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof; and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." In particular, EDWARDS fails to disclose such methods

wherein a complex of proteins and sulfated polysaccharides are encapsulated within a matrix of hydrophobic material for preparation of a sustained release solid protein drug.

In contrast, EDWARDS discloses particles incorporating (1) a surfactant and/or (2) a hydophobic or hydophilic complex of a positively or negatively charged therapeutic agent (including proteins) and a charged molecule of opposite charge for drug delivery to the pulmonary system. Furthermore, EDWARDS does not teach the combination of recited steps as claimed.

For at least the reasons set forth above, EDWARDS fails to fairly suggest the claimed invention.

In view of the foregoing remarks, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, and respectfully request withdrawal of the rejection under 35 U.S.C. 103(a).

The Office Action also rejects claims 1-2, 4-8, 10-14, and 16-17 under 35 U.S.C. § 103(a) as allegedly unpatentable over EDWARDS in view of STRAUB. In particular, the Office Action states that EDWARDS is silent with regard to forming the particles described therein in a non-aqueous solution. For this missing feature the Office relies upon STRAUB.

In response, and without acquiescing to the propriety of any of the assertions made in the rejection of the claims under 35 U.S.C. § 103(a), Applicants respectfully submit that the amendment addresses the instant rejection and respectfully request withdrawal of the same. Applicants further submit that the claimed subject matter is not unpatentable over EDWARDS in view of STRAUB for at least the reasons set forth above. In particular, Applicants submit that

EDWARDS and/or STRAUB, either alone or in any reasoned combination, do not disclose "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide,

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof, and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein." Neither do EDWARDS and/or STRAUB, either alone or in combination disclose or fairly suggest "[a] process to prepare a sustained release solid protein drug consisting essentially of:

(a) preparing a mixture of a protein and a sulfated polysaccharide at room temperature to form a complex of the protein and the sulfated polysaccharide, and further adding a protein stabilizer to the mixture;

(b) suspending the mixture obtained in (a) in a solution containing hydrophobic materials selected from fatty acids, pamoic acid, monoacyl glycerols, sorbitan fatty acid esters, diacyl glycerols, triglycerides, phospholipids, sphingosines, sphingolipids, waxes, and salts or derivatives thereof; and

(c) removing a solvent from the suspension to obtain a solid protein drug;

wherein the pH of the mixture of the protein and the sulfated polysaccharide is lower than the isoelectric point of the protein."

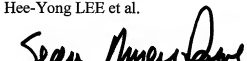
For at least the reasons set forth above, EDWARDS and/or STRAUB, either alone or in any combination, fail to fairly suggest the claimed invention.

In view of the foregoing remarks, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, and respectfully request withdrawal of the rejection under 35 U.S.C. 103(a).

Conclusion

In view of the foregoing remarks and amendments, Applicants respectfully submit that the claims are in condition for allowance. If there should be any questions, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,
Hee-Yong LEE et al.



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